REMARKS

At the outset, Applicant thanks the Examiner for extending his search for relevant art to include ***all*** species recited in claims 40-42, 45, 63, 67, and 68.

I. Amendments to the Claims:

Claims 15-23, 25-33, 35-60, 63-68 and 72-76 are pending in this application.

Claims 16-23, 25-29, 37, 38, and 72-74 have been withdrawn from consideration as being drawn to non-elected claims.

Claim 41 has been amended to capitalize the trademarks recited therein.

Upon entry of the instant amendment, claims 15, 30-33, 35, 36, 39-60, 63-68, 75, and 76 will be pending in the instant application.

II. Amendments to the Specification:

The specification has been amended to update the status of applications to which the instant application claims priority. In addition, the specification has been amended to capitalize trademarks.

III. Priority:

Applicant provides herewith as **Appendix A** and **Appendix B** certified copies of the PP9778 and PRO745 applications filed in Australia.

IV. Rejection Under 35 U.S.C. § 112, Second Paragraph:

Claim 15 stands rejected under 35 U.S.C. § 112, second paragraph, as purportedly being indefinite. Specifically, the Office Action alleges that claim 15 is incomplete for omitting a resolution step that sets forth how to reactivate a patient's thymus.

Applicant respectfully traverses this rejection for the following reasons.

As a preliminary matter, Applicant avers that by requiring Applicant to recite a specific method for reactivating the thymus in claim 15, the Office Action has improperly invited the

Applicant to narrow the scope of claim 15 by adding the limitations of claims 30, and/or 37-42. Applicant respectfully declines this invitation because claim 15 as currently pending is definite.

According to MPEP § 2173.02, definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(i) the content of the particular application disclosure;

(ii) the teachings of the prior art; and

(iii) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In the instant case, Applicant respectfully avers that the application-as-filed very clearly explains how to reactivate the patient's thymus. In this regard, Applicant draws the Examiner's attention to, for example, page 9, lines 23-30; page 30, line 23 to page 31, line 2; page 33, line 26 to page 34, line 17; Example 6; Example 8; page 114, line 15 to page 115, line 2; Example 14; and Example 17 of the application-as-filed. These sections of the application clearly set forth how the thymus may be reactivated.

Moreover, Applicant notes that the Office Action by its very own statements has admitted that the recitation "reactivating the thymus of the patient" is clear and definite:

> The specification only discloses data of enhanced regeneration of thymus of castrated mice. In said experiments ***thymus has been reactivated by removing the effects of sex steroid on the the thymus after surgical castration.*** (*see,* Office Action, page 4 , last paragraph) (emphasis added).

> The specification does not adequately teach how to effectively improve an immune response to a vaccine antigen in a patient, comprising reactivating the thymus, claimed in claim 15, ***wherein reactivating is by disrupting of sex-mediated signaling to the thymus claimed in claim 30, by administration of one or more pharmaceutical, wherein pharmaceutical are recited in claims 40, 41, and 42***...(see, Office Action, page 5, first full paragraph) (emphasis added).

These statements in the Office Action evidence that the Examiner is aware of what is meant by "reactivating the thymus of the patient" as recited in claim 15.

In view of the foregoing remarks, Applicant respectfully requests that this rejection under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

V. Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement:

Claims 15, 30-33, 35, 36, 39-60, 63-68, 75, and 76 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabling. Briefly, the enablement rejection set forth in the Office Action purports the following:

(i) the specification provides no animal model data or other working examples showing the effectiveness of the claimed method;

(ii) Applicant has acknowledged that the efficacy of the claimed method for improving an immune response to a vaccine antigen has not even been established for a mouse model; and that

(iii) the specification provides no information on the immunogenicity of any vaccine antigen.

Applicant respectfully traverses this rejection for the reasons articulated below.

The sole independent claim pending in the instant application is directed to a method for improving an immune response to a vaccine antigen in a patient. The method comprises reactivating the thymus of the patient, and administering a vaccine to the patient, wherein the vaccine comprises a vaccine antigen. The method results in the patient developing an improved immune response to the vaccine antigen. Applicant respectfully avers that the pending claims are fully enabled by the application-as-filed.

Regarding point (i) set forth above, Applicant respectfully avers that there is no statutory requirement for working examples, including animal model data, for a disclosure to be enabling. It is a well-established principle in U.S. patent law that an Applicant need not have actually reduced the invention to practice prior to filing (*see, Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)). In fact, MPEP § 2164.02 states that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed.

In the instant application, Applicant has provided several prophetic examples, using mouse models, directed to improvement of immune response to a vaccine antigen, comprising reactivating the thymus of the patient. For example, Example 9, at pages 92-99, provides a

method for immunizing against viral infections (*e.g.*, influenza); Example 10, at pages 100-103, is directed to methods for immunizing patients against parasitic infection (*e.g.*, malaria); Example 11, at pages 104-107, relates to methods of immunizing patients against bacterial infections (*e.g.*, *Mycobacterium tuberculosis*); and finally, Example 12, at pages 107-108, is directed to methods for immunizing patients against cancer. These prophetic examples provide significant guidance to one of ordinary skill in the art to practice the claimed invention.

For example, Example 9 provides sufficient detail for treating a subject undergoing influenza vaccination with sex steroid inhibition to reactivate the thymus and improve the status of a patients T cells, thereby resulting in an enhanced response to the influenza vaccination. Background is given on the major epitopes of the virus highlighting those which vary between infectious rounds as a result of genetic drift within a subtype, *e.g.*, H3, and antigenic shift with a change of one subtype to another. Both these phenomena are important in vaccine design, as is well known in the field of flu vaccine preparation. The methods known to produce various types of vaccine are referenced in the example and routes of administration are also considered. However, Applicant notes that vaccine production is not the subject of the invention, and the disclosure merely illustrates that T cell responses to a range of vaccine types can be enhanced with the subject invention. Although it would be apparent to a clinical immunologist, mention is made of the importance of both cytotoxic T cells and circulating antibodies, both of which depend on T helper cells. Information for clinical translation is provided with the dose and type of LHRH (GnRH) for chemical castration, based on the current use in the clinic for males (prostate cancer) or females (endometriosis). Reference is also made to well-known methods to measure castrate levels and determine whether sex steroid levels have been reduced. Information is also provided on the expected timing to castrate levels of sex steroids. The timing of the vaccination schedule relative to the impact of castration is also clearly described. As known to the clinical immunologist, cytokines that skew the immune response towards Th1 (cell-mediated immunity) or Th2 (Ab-mediated immunity) are described. Details are provided for testing the efficacy of the vaccine and improvement therein with castration by subsequent challenge. This is more relevant in the pre-clinical models because

opportunistic infection of humans is the clinical experience; however, extensive details are provided on the methods for measuring immune response, which should all be known to the clinical immunologist. The basic concept provided is adequate to teach the application of the invention in respect of any known vaccine, as all vaccines function by stimulating a primary (and in some cases secondary) immune response, such that the subject is primed to respond more rapidly and effectively to subsequent exposure to challenge. That challenge may come in many forms, such as virus, bacteria, parasite, toxin, or cancer, but the concept is unchanged, regardless of the source of antigen.

In prophetic Example 10, the application of the present invention to another type of infectious agent, malaria, is described. However, the method of the invention remains unchanged, only the vaccine described and methods for testing response change. For *Plasmodium yoelii* (*P. yoelii*) infection in mice, passive transfer *P. yoelii* CSP-specific monoclonal antibodies as well as adoptive transfer of *P. yoelii* CSP-specific $CD8^+$ T cells are protective. The appropriate references for this are cited in the prophetic example. The clinical immunologist is given an extensive list of potential sporozoite proteins that could be used. As described above, the means of improving thymic function and, hence, T cells by chemical castration are provided, again based on the dosage of LHRH currently used in the clinic for males (prostate cancer) or females (endometriosis). The clinical immunologist is also provided with all the necessary information for vaccination and for monitoring the changes in the immunological parameters and their improvement by loss of sex steroids.

In prophetic Example 11, the use of the invention in improving the immune response of a vaccine to a bacterial antigen is described. The immune response required for protection against bacterial infection again requires T helper cells to co-induce B cells to produce antibodies, but also the Th cells themselves. A wide variety of potential antigens are provided for the clinical immunologist; the predominant T cell antigens of tuberculosis (TB) are those proteins that are secreted by mycobacteria during their residence in macrophages. Details are given for the preparation of the vaccine and the vaccination schedule, including use of an adjuvant. In particular, information is provided for DNA vaccination to the important Ag85

epitope. Again, the details for boosting thymic function and generation of new T cells by chemical castration are also provided, and it should be noted that these are unchanged from the previous examples, as the method of the invention is not dependent upon the vaccine being used.

In prophetic Example 12, the application of the invention in cancer treatment is described. Since cancer by definition is a disease of "self" and cannot be contracted from someone else (unless it is viral induced, *e.g.*, HPV), the immune response to cancer is often very poor (since the immune system is programmed to not react against self). Furthermore, prolonged exposure to the cancer can deplete the immune system of any potentially-reactive cells (through antigen-induced cell death) and the cancer can deliver a non-stimulatory signal to the immune system which induces a state of tolerance. Hence, all these features, coupled with the age-dependent decline in thymic output and T cell function with age, lead to the major clinical problem that immunity to cancer is very poor. Any potential boost to the immune system is, therefore, extremely important for improving the outcome of vaccination to cancers. In this prophetic example, the clinical immunologist is given the details for boosting thymic and T cell function by chemical depletion of sex steroids. The antigen of focus is Carcino Embryonic Antigen (CEA) which is expressed on many cancer (and embryonic) cells, but rarely in normal adult tissue. Details are given for the human CEA gene (MC 38-CEA-2); success of the vaccination is determined by challenge with a syngeneic tumor cell line expressing the same CEA antigen – of course, this is not necessary in the clinic. Clinical success of the effect of chemical castration on the vaccination schedule would be provided by monitoring of the cancer status (*e.g.*, incidence and severity of clinical relapse).

Notwithstanding the four examples discussed above, Applicant further notes that the specification discloses the claimed invention in a manner that one of ordinary skill in the art will be able to practice without an undue amount of experimentation.

More specifically, the specification describes at page 10, line 14 to page 11, line 3, the methods for improving a patient's immune response to a vaccine are accomplished by quantitatively and qualitatively restoring the peripheral T cell pool, particularly at the level of

naïve T cells. These naïve T cells are then able to respond to a greater degree to presented foreign antigen. A patient's immune response to a vaccine may be improved by causing the patient's thymus to reactivate and the functional status of the peripheral T cells to be improved. In this instance, the thymus will begin to increase the rate of proliferation of the early precursor cells ($CD3^-CD4^-CD8^-$ cells) and convert them into $CD4^+CD8^+$, and subsequently new mature $CD3^{hi}CD4^+CD8^-$ (T helper (Th) lymphocytes) or $CD3^{hi}CD4^-CD8^+$ (T cytotoxic lymphocytes (CTL)). The rejuvenated thymus will also take up new haemopoietic stem cells (HSC) from the blood stream and convert them into new T cells and intrathymic dendritic cells. The increased activity in the thymus resembles that found in a normal, younger thymus (prior to the atrophy at ~20 years of age). The result of this renewed thymic output is increased levels of naïve T cells (those T cells which have not yet encountered antigen) in the blood. There is also an increase in the ability of the blood T cells to respond to stimulation, *e.g.*, by using anti-CD28 Abs, cross-linking the TCR with, *e.g.*, anti-CD3 antibodies, or stimulation with mitogens, such as pokeweed mitogen (PWM). This combination of events results in the body becoming better able to respond to vaccine antigens, thereby ultimately being able to better defend against infection and other immune system challenges (*e.g.*, cancers), or becoming better able to recover from chemotherapy and radiotherapy.

Applicant also draws the Examiner's attention to the additional disclosure provided at page 7, line 10 to page 9, line 30; and page 57, line 15 to page 59, line 3. Taken together, these sections of the application-as-filed provide specific and detailed guidance of how to effectively practice the invention as presently claimed.

Applicant notes that the predecessor court of the Federal Circuit held that a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re*

Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis added). As stated by the court,

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. 439 F.2d at 224, 169 USPQ at 370.

In the instant case, Applicant respectfully avers that the Patent Office has not met the burden imposed upon it by the Court.

The Examiner relies on Feldman *et al.*, Windmill *et al.*, and Applicant's disclosure to argue that the basis for thymic hypertrophy is complex. Applicant fully agrees. However, as the Examiner is aware, mechanisms of action are not necessary for an invention to be deemed patentable. Furthermore, Applicant's claims are not directed to explaining the detailed scientific mechanism for thymic reactivation. Rather, Applicant's claims are directed to methods for improving a patient's immune response to a vaccine antigen, regardless of how the thymus reactivates in the absence of sex-steroid inhibition.

With respect to point (ii) set forth above, Applicant notes that the conclusion drawn by the Examiner based on the last sentence of page 103 is incorrect. The specification does not, as the Office Action alleges, explicitly stress or acknowledge that the efficacy of the claimed method for improving an immune response to a vaccine antigen has not even been established for a mouse model.

The last sentence on page 103 belongs to Example 10; Example 10 is a prophetic example. As the Examiner is aware, a prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved. Clearly then, Applicant could not have indicated that results had been achieved in mice without the experiment actually having been done or completed. Thus, the sentence referred to by the Examiner does not indicate that the claimed method does not work in mice and/or humans.

Finally, with respect to point (iii) set forth above, Applicant notes that the claimed invention is not directed to developing new vaccines, but improving the efficacy of vaccines. In any event, Applicant notes that methods for assessing the effectiveness of a vaccine were well known in the art at the time the instant application was filed. In this context, it is noteworthy that the Federal Circuit has held that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984) (emphasis added). Nevertheless, Applicant draws the Examiner's attention to the disclosure in the prophetic examples in the instant application, which provides methods for assessing the effectiveness of a vaccine by measuring antibody and cell-mediated responses (*see*, Examples 9-12).

In light of the foregoing remarks, Applicant respectfully submits that he has fully enabled the invention as claimed.

Although the above arguments are more than sufficient to overcome this rejection, Applicant also provides a Declaration Under 37 C.F.R. § 1.132 to further evidence that the invention as claimed is fully enabled (*see*, **Appendix C**).

In view of the foregoing, Applicant respectfully requests that this rejection under 35 U.S.C. § 112, first paragraph, enablement, be reconsidered and withdrawn.

VI. Rejections Under Non-Statutory Obviousness-Type Double Patenting:

Claims 15, 30-33, 35, 36, 39-60, 63-68, 75, and 76 stand provisionally rejected under the doctrine of non-statutory obviousness-type double patenting as being unpatentable over the claims of U.S. Appl. Nos. 10/339,213; 10/418,727; 10/418,747; 10/749,119; 10/419,039; 10/749,120; 11/296,676; 10/748,831; 10/749,122; 10/553,594; and 10/553,608.

As a preliminary matter, Applicant notes that U.S. Appl. Nos. 10/339,213; 10/418,727; 10/418,747; and 10/419,039 have been abandoned. Accordingly, the above rejection as it relates to these applications is moot.

Applicant respectfully requests that the provisional rejection as it relates to the remaining applications be held in abeyance until such time as allowable subject matter is indicated in the instant application.

CONCLUSIONS

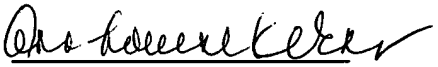
Upon entry of this amendment, claims 15-23, 25-33, 35-60, 63-68 and 72-76 are pending and under examination in this application.

Applicant petitions for a 3-month extension of time to respond to the outstanding Office Action. Please charge our Deposit Account No. 08-0219 for the 3-month extension of time fees. Other than these fees, and the fees associated with the filing of the Supplemental IDS, no additional fees are due. However, if any fees are due, please charge the requisite fees due to our Deposit Account No. 08-0219.

If a telephone interview would advance prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,

Dated: October 10, 2006



Ann-Louise Kerner, Ph.D.
Reg. No. 33,523

WILMER CUTLER PICKERING HALE AND DORR LLP
60 State Street
Boston, MA 02109
Tel.: (617) 526-6192
Fax: (617) 526-5000